DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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James H. Lee, M.D., Ph.D.
Chief Medical Officer
Graceway Pharmaceuticals, LLC
222 Valley Creek Boulevard, Suite 300
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Re: Docket No. FDA-2009-P-0423

Dear Dr. Lee:

This letter responds to your citizen petition received on August 28, 2009 (the Petition), concerning applications for generic versions of Aldara (imiquimod) Cream, 5%.[1] You state that you believe there are at least two pending applications for generic versions of Aldara from Altana Inc. (now Nycomed US Inc. (Nycomed))[2] and Perrigo Israel Pharmaceuticals Ltd. (Perrigo) that propose to substitute oleic acid, either alone or in combination with other ingredients, for the isostearic acid used in the Aldara formulation (Petition at 1 and 2).[3] You claim oleic acid is a "known skin irritant" and may also increase systemic absorption of imiquimod, Aldara's active ingredient (Petition at 1). Accordingly, you request that the Food and Drug Administration (FDA or the Agency) refuse to approve any application for a new drug that relies on Aldara as the listed drug and substitutes another ingredient (or ingredients) for isostearic acid unless the applicant has demonstrated that such substitution does not affect the safety of the drug product by providing data from (1) preclinical testing of the excipient, vehicle, and final product formulation; (2) clinical testing of the skin irritation and sensitization of the formulation; and (3) a maximal use pharmacokinetic study in patients with external genital and perianal warts as well as a maximal use pharmacokinetic study in patients with actinic keratoses (Petition at 2).

[1] You previously submitted a citizen petition concerning bioequivalence requirements for generic versions of Aldara drugs which we denied (Letter from Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA, to Dr. James Lee, Graceway Pharmaceuticals, LLC (Jan. 26, 2010) (Aldara BE Petition Response)). We will refer to that petition as the Aldara BE Petition and this petition as the Aldara Oleic Acid Petition or simply the Petition.

[2] Altana was purchased by Nycomed and renamed Nycomed US Inc. In this response, we will refer to this applicant as Nycomed.

[3] You state that you submitted this Petition 180 days before any generic version of Aldara could obtain final approval (Petition at 2, footnote 1), and you state that February 25, 2010, is the date that such final approval could first be granted (Petition at 17, footnote 72). We point out, however, that our 180-day deadline to respond to your Petition (per section 505(q) of the Federal Food, Drug, and Cosmetic Act) falls on February 24, 2010. Accordingly, because we cannot reveal any non-public information concerning any pending ANDAs for generic versions of Aldara, and because we will not make determinations regarding any specific aspect of a pending ANDA outside of the normal application process, our response to your Petition only addresses your requests generally, and should not be construed as reaching any specific conclusions regarding any pending ANDA or NDA or any aspect of such application. Those decisions are made in the normal course as part of FDA's review of any drug application.

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You further contend that, in light of these purported data requirements, applications for generic versions of Aldara are not suitable for the abbreviated new drug application (ANDA) process specified at section 505(j) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act). Accordingly, you request that the Agency refuse to approve the Nycomed and Perrigo applications (and any other similarly situated application) under 505(j) of the FDCA and require them to be submitted as new drug application (NDAs) instead under section 505(b)(2) of the FDCA (Petition at 2).

We have carefully considered the Petition. For the reasons stated below, the Petition is denied.

I. BACKGROUND

A. Aldara (imiquimod) Cream, 5%

Graceway Pharmaceuticals, LLC, is the holder of the new drug application (NDA 020723) for Aldara (imiquimod) Cream, 5%. Aldara is a topical cream with three approved indications. Aldara was initially approved in 1997 for the treatment of external genital and perianal warts/condyloma acuminata (EGW) in patients 12 years or older. EGW is a sexually transmitted disease caused by infection with certain strains of the human papillomavirus. In 2004, Aldara was approved for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic[4] actinic keratoses (AK) on the face or scalp in immunocompetent adults. Also in 2004, Aldara was approved for the topical treatment of biopsy-confirmed, primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maximum tumor diameter of 2.0 centimeters, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured. AK and sBCC are abnormal proliferations of cells that arise within the epidermis below the stratum corneum (the outermost layer of skin).

Aldara contains 5% imiquimod (the active ingredient) and, among other inactive ingredients, 25% isostearic acid. Isostearic acid is used to solubilize the active ingredient and to aid drug penetration through the outer layer of skin.

B. ANDAs for Aldara

You state that on January 16, 2007, Graceway received notice that Nycomed had submitted an ANDA for a generic version of Aldara that formulated around Patent No. 5,238,944 (the '944 Patent) by substituting 25% oleic acid for the isostearic acid in Aldara's formulation (Petition at 4). You also state that on or about June 29, 2007, Graceway received notice that Perrigo had submitted an ANDA for a generic version of Aldara and formulated around the '944 Patent by eliminating isostearic acid from the formulation. You state that a patent application indicates

[4] Hyperkeratosis is thickening of the stratum corneum (the outermost layer of skin). Hypertrophy is an increase in the size of a cell.

that the Perrigo product may contain a minimum of 7.4% oleic acid and other inactive ingredients in place of isostearic acid (Petition at 4).

C. Applicable Statutory and Regulatory Framework

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Act, which established the current ANDA approval process. To obtain approval, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of the drug product; instead an ANDA applicant relies on FDA's previous finding that the reference listed drug (RLD)[5] is safe and effective. An ANDA applicant for a generic[6] drug must identify a RLD on which it seeks to rely and, with limited exceptions, a drug product described in an ANDA must contain the same active ingredient,[7] conditions of use,[8] route of administration, dosage form, strength,[9] and (with certain permissible differences) labeling[10] as the listed drug it references (sections 505(j)(2)(A) and (j)(4) of the Act). The applicant must also demonstrate that the proposed drug product is bioequivalent to the RLD (section 505(j)(2)(A)(iv) of the Act).[11]

This Petition concerns inactive ingredients in generic topical drugs. With few exceptions, the inactive ingredients in generic drug products need not match those in the RLD.[12] For drugs intended for oral use, the applicant must "identify and characterize the inactive ingredients in the proposed drug product and provide information demonstrating that such inactive ingredients do not affect the safety or efficacy of the proposed drug product" (21 CFR 314.94(a)(9)(ii)). For topical drugs, the applicant can use different inactive ingredients if the applicant "identifies and characterizes the differences and provides information demonstrating that the differences do not

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[5] A reference listed drug or RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs are identified in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, generally known as the "Orange Book."

[6] For purposes of this response, the term generic drug refers to new drug products for which approval is sought in an ANDA submitted under section 505(j) of the Act.

[7] See, e.g., 21 CFR 314.94(a)(5).

[8] See, e.g., 21 CFR 314.94(a)(4).

[9] See, e.g., 21 CFR 314.94(a)(6).

[10] See, e.g., 21 CFR 314.94(a)(8).

[11] See, e.g., section 505(j)(2)(A)(iv) of the Act (requiring "information to show that the new drug is bioequivalent to the listed drug"); 21 CFR 314.3 (defining reference listed drug); 21 CFR 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the reference listed drug); and 21 CFR 314.127(a)(6)(i) (providing that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the ANDA).

[12] Generic versions of drugs intended for otic, ophthalmic, or parenteral (i.e., injectable) use are subject to different requirements regarding inactive ingredients; subject to certain exceptions, the inactive ingredients in generic versions of these products must match those in the RLDs (21 CFR 314.94(a)(9)(iii)-(iv)).

affect the safety or efficacy of the proposed drug product" (21 CFR 314.94(a)(9)(v)).[13] Thus, the standard for inclusion of inactive ingredients in a proposed generic drug product that differ from those in the RLD is the same for a topical drug as it is for a drug intended for oral use — the applicant must show they do not affect the safety or efficacy of the product.

The Agency must refuse to approve an ANDA (for a topical product or any other product) if it determines that "the inactive ingredients of the drug are unsafe for use" as labeled, or if "the composition of the drug is unsafe for use under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included" (section 505(j)(4)(H) of the Act; see also 21 CFR 314.127(a)(8)(i)). The Agency considers the inactive ingredients or composition of a proposed generic drug product unsafe "if, on the basis of information available to the agency, there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raises serious questions of safety or efficacy" (21 CFR 314.127(a)(8)(ii)(A)).

Accordingly, an ANDA applicant for a topical product that seeks to use one or more inactive ingredients not found in the RLD must demonstrate that the proposed changes do not affect the safety of the product, and the Agency must determine that the proposed changes do not raise "serious questions of safety or efficacy." As with all of the Agency's technical and scientific conclusions concerning the safety and efficacy of drugs and drug ingredients, the Agency's judgments concerning what the applicant must do to satisfy its burden, what constitutes a "serious question of safety," and what information it can or should rely on to reach these judgments are matters that "fall squarely within the ambit of the FDA's expertise and merit deference" from the courts (*Schering Corp. v. FDA*, 51 F.3d 390, 399 (3rd Cir. 1995)).[14]

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[13] The Agency originally proposed requiring all applicants for generic drugs to include such a comparison of inactive ingredients, but the Agency received objections pointing out that an ANDA applicant for a drug product intended for oral use might not be able to discover what inactive ingredients were included in the RLD because inactive ingredients are not generally required to be listed on the label for such products (21 CFR 201.100(b)(5)). Accordingly, the Agency decided to require such a comparison of inactive ingredients only for drug products intended for topical, otic, ophthalmic, or parenteral use because such ingredients are required to be disclosed on the labeling for those categories of drug products (Preamble to Abbreviated New Drug Application Regulations, 57 FR 17950 ¶ 44 (April 28, 1992)).

[14] Two appellate courts have considered, and rejected, challenges to the Agency's determinations regarding the safety of inactive ingredients in generic parenteral (injectable) drug products. See *Zeneca Inc. v. Shalala*, 213 F.3d 161, 170 (4th Cir. 2000) (affirming FDA's determination that certain studies were sufficient to demonstrate safety of generic version of parenteral drug product containing different inactive ingredients than the RLD); *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313, 1324 (3rd Cir. 1998) (affirming FDA's reliance on animal studies to confirm safety of inactive ingredients in generic parenteral drug product that differed from RLD). With limited exceptions, only certain categories of inactive ingredients (preservatives, buffers, or antioxidants) in parenterals may be altered — all others must be the same as those contained in the RLD, a restriction not applicable to topical drug products (compare 21 CFR 314.94(a)(9)(iii) with 21 CFR 314.94(a)(9)(v)). Furthermore, the Agency presumes that "any inactive ingredient in a [generic] applicant's proposed [parenteral] drug product different from that in the reference listed drug to be unsafe unless the applicant can rebut the presumption by demonstrating that the different inactive ingredient will not affect the safety [or efficacy] of its proposed drug product" (54 FR 28872 at 28884, July

II. DISCUSSION

In the Petition, you assert that an applicant for a generic version of Aldara Cream that proposes to substitute another ingredient (or ingredients) for the isostearic acid used in the Aldara vehicle should be required to provide data from certain studies to demonstrate the safety of such a formulation change. The Petition primarily focuses on the proposed substitution of oleic acid for isostearic acid. You claim that including oleic acid in the formulation of a generic version of Aldara "raise[s] potential safety risks, both because of the possible effect on systemic absorption [of imiquimod] and because oleic acid is a known skin irritant" (Petition at 1, 7-8). You further claim that the safety of oleic acid as a pharmaceutical excipient in topical cream drug products, or in any drug product at concentrations above 7.4%, cannot be adequately assessed by reference to existing data, scientific literature, or Agency experience with previously approved drugs (Petition at 8-10). Accordingly, you contend that applicants for generic imiquimod products must provide extensive data from (1) preclinical testing of the excipient, vehicle, and final product formulation; (2) clinical testing of the skin irritation and sensitization of the formulation; and (3) a maximal use pharmacokinetic study in patients with external genital and perianal warts as well as a maximal use pharmacokinetic study in patients with actinic keratoses (Petition at 2, 10-15). You further contend that because data from animal and clinical investigations are necessary to demonstrate the safety of oleic acid in the Nycomed and Perrigo proposed products, the ANDA process is not the appropriate pathway for their products. Rather, you claim that Nycomed, Perrigo, and any other similarly situated applicants must seek approval under the section 505(b)(2) pathway instead (Petition at 15-16).

As explained below, however, we have concluded that an applicant for a generic version of Aldara containing up to 25% oleic acid in place of isostearic acid could demonstrate the safety of the proposed drug product without conducting the animal or human clinical studies that you contend are required. Accordingly, we further disagree that applications for such products may only be approved through the 505(b)(2) pathway.[15]

10, 1989). The Agency does not apply a similar presumption to substituted inactive ingredients in generic topical drug products.

[15] On page 2 of the Petition you also request that we apply the testing you propose to applications submitted pursuant to section 505(b)(2) of the Act that rely on Aldara as the listed drug and that substitute another ingredient (or ingredients) for isostearic acid. A 505(b)(2) application relies, at least in part, on data and information not owned by the applicant and to which the applicant does not have a right of reference. Requirements for approval of 505(b)(2) applications differ from requirements for approval of ANDAs. The Petition focuses on an application for a generic product that differs from Aldara only with respect to a change in inactive ingredients, and in particular with respect to the substitution of oleic acid for isostearic acid. Because the appropriate vehicle for approval of such a product is, as discussed in the text, an ANDA, the question of requirements for a 505(b)(2) application does not arise.

The issue of requirements for a 505(b)(2) application would only arise if the drug in question differed from the listed drug in other respects. Drug products proposed in applications submitted via the 505(b)(2) pathway can differ from listed drugs in a variety of ways. What safety data or information the Agency may require for such applications may vary from application to application based on the specifics of the particular drug product. Furthermore, your Petition does not discuss any particular (actual or hypothetical) imiquimod products that might be submitted as

A. Inclusion of Up To 25% Oleic Acid in Generic Versions of Aldara Does Not Raise Safety Concerns.

For the reasons described below, we conclude that, as a general matter, we have no reasonable basis to conclude that up to 25% oleic acid in a generic version of Aldara raises serious questions of safety. In particular, we disagree with your assertions regarding oleic acid's skin irritation properties and properties as a penetration enhancer. We further conclude that an applicant could provide sufficient data and information through the normal ANDA process to adequately demonstrate the safety of such a change in any specific proposed generic drug product.[16]

1. Oleic acid's skin irritation properties do not raise serious safety concerns

You claim that oleic acid is a "known irritant" that, based on histological scoring in one study in hairless mice, "caused unacceptably severe damage to the skin" (Petition at 7-8). While you acknowledge that "the relevance of this model in predicting the response in patients is not known," you claim that "it indicates the existence of potential risks associated with the use of oleic acid in a topical cream that an applicant must address" (Petition at 8). You further claim that the presence of oleic acid in many previously approved drug products and in the Agency's Inactive Ingredients Database is insufficient to allay concerns about these "potential risks" (Petition at 8-9).

We disagree with your assertions. We believe that the scientific literature, prior Agency experience with oleic acid as an inactive ingredient in many approved drug products, and the extensive use of oleic acid in cosmetics, together with data and information submitted with any ANDA for a generic version of Aldara containing oleic acid, could be sufficient to satisfy the Agency that up to 25% oleic acid in imiquimod formulations is safe.[17]

505(b)(2) applications. We therefore decline to speculate on what safety data or information would be needed for the wide spectrum of 505(b)(2) applications that could potentially be submitted. Accordingly, this response will not address your request regarding 505(b)(2) applications for imiquimod products, except to conclude that a generic version of Aldara that differs from Aldara only in that oleic acid is substituted for isostearic acid is appropriately considered under an ANDA, not under a 505(b)(2) application.

[16] All ANDAs are reviewed on a case-by-case basis Thus, an application that failed to demonstrate to our satisfaction that any new inactive ingredients did not affect the safety or effectiveness of the proposed product would not be approved.

[17] As noted above, an ANDA applicant must characterize any inactive ingredients in its proposed topical drug product that differ from those in the RLD and demonstrate that those differences do not affect the safety or efficacy of the product (21 CFR 314.94(a)(9)(v)). Furthermore, the Agency must refuse to approve an ANDA "if, on the basis of information available to the agency, there is a reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raises serious questions of safety or efficacy" (21 CFR 314.127(a)(8)(ii)(A)). While your Petition focuses exclusively on safety concerns (Petition at 5, footnote 18), we point out that an ANDA applicant for a topical drug product must show that any inactives that are different from the RLD do not affect either the safety *or the efficacy* of the proposed drug product.

First, our thorough review of the relevant scientific literature indicates that oleic acid is generally non-irritating in humans.[18] The study in hairless mice you rely upon is not pertinent because it was an occlusion study — a 10% oleic acid solution was kept in contact with the skin of hairless mice using cups taped and glued to the skin.[19] Occlusion alone may damage skin barrier function by obstructing normal ventilation of the skin surface and increasing stratum corneum hydration.[20] Further, when chemicals or drugs are applied under occlusive conditions we expect increased penetration of chemicals and antigens into the skin and increased dermatitis.[21] More important, the study was conducted in hairless mice – not humans. Many human irritation tests of oleic acid conducted or reviewed as part of the Cosmetic Ingredient Review (CIR) review of oleic acid showed little to no dermal irritation.[22]

Second, oleic acid is an inactive ingredient in many previously approved drug products including topical or transdermal products (one of which, like Aldara, is a semi-solid product).[23] Thus, the Agency has extensive experience and data demonstrating the safety of oleic acid as a pharmaceutical excipient, in topical preparations and otherwise.

Next, while you are correct that we have not previously approved a topical product containing oleic acid at a concentration higher than 7.4% (Petition at 8), we do not think that the inclusion of up to 25% oleic acid in the formulation of a generic version of Aldara raises any serious safety concerns. Oleic acid is found in hundreds of topical cosmetic products, sometimes at concentrations up to 50%,[24] and an expert panel of the CIR industry program deemed oleic acid safe at such concentrations.[25] Oleic acid is also found in many vegetable oils,[26] food additives,

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[18] See Final report on the safety assessment of oleic acid, lauric acid, palmitic acid, myristic acid, and stearic acid. (Cosmetic Ingredient Review). *J Am Coll Toxicol.* 1987; 6(3): 321-401.

[19] Lashmar UT et al., Topical application of penetration enhancers to the skin of nude mice: a histopathological study. *J Pharm Pharmacol.* 1988: 41; 118-121 (attached to Petition at Tab 13).

[20] Zhai H and Maibach HI Occlusion and barrier function, in Zhai H and Maibach HI, Eds. *Dermatotoxicology.* 6th Ed., 2004; 13-28.

[21] Zhai H and Maibach HI. 13-28.

[22] Final report on the safety assessment of oleic acid, lauric acid, palmitic acid, myristic acid, and stearic acid. (Cosmetic Ingredient Review). *J Am Coll Toxicol.* 1987; 6(3): 321-401. You cite a study in humans which found that oleic acid is a "severe irritant" when combined with 20% propylene glycol. See Loftsson T et al., The effect of vehicle additives on the transdermal delivery of nitroglycerin. *Pharm Research.* 1987: 4(5); 436. We do not think this study is pertinent, however, because, like the hairless mice study, it was also an occlusion study. The Loftsson study further found that "no irritation could be detected when pure oleic acid or pure propylene glycol was applied to the skin under occlusion for 6 hr." See id. at 436-37.

[23] See FDA Inactive Ingredient Database available at http://www.accessdata.fda.gov/Scripts/cder/iig.

[24] Cosmetic Ingredient Review at www.cir-safety.org, and Quick Reference Table (Cosmetic Ingredient Review), available at http://www.cir-safety.org/staff_files/pdf4.pdf (on pg. 43 of 70).

[25] Final report on the safety assessment of oleic acid, lauric acid, palmitic acid, myristic acid, and stearic acid. (Cosmetic Ingredient Review). *J Am Coll Toxicol.* 1987; 6(3): 321-401. CIR reaffirmed its conclusion regarding the safety of oleic acid in June 2005. Annual review of cosmetic ingredient safety assessments – 2004/2005. *Int J Toxicol.* 2006; 25 (Suppl 2):1-89.

animal fats, shampoos, lotions, and cosmetics. Meat, poultry, and fish are also major sources of oleic acid. In fact, we anticipate that the amount of oleic acid present in the average person's daily food supply would be several orders of magnitude greater than the amount contained in a 250 milligram (mg)/foil packet of Imiquimod Cream 5% containing 25% oleic acid.[27] Furthermore, oleic acid, along with several other fatty acids, is approved as a direct food additive with no limitations other than good manufacturing practices (21 CFR 172.860).

While it is true that neither cosmetics nor foods are "regulated to the same standards as drugs" (Petition at 8, footnote 34), this does not mean that we cannot consider the presence of an inactive ingredient in cosmetic products or in the food supply in determining what additional safety studies may be necessary.[28] Indeed, we see no reason not to consider this information. As we explain in the FDA guidance for industry, *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients* (hereinafter Excipients Guidance) (at 2) (updated May 2005)[29], in some circumstances an excipient's presence in food, cosmetics, or previously approved products will be sufficient to fully qualify the safety of the ingredient:

> [CDER and CBER] recognize that existing human data for some excipients can substitute for certain nonclinical safety data, and an excipient with documented prior human exposure under circumstances relevant to the proposed use may not require evaluation in the full battery of toxicology studies outlined in this guidance. For example, [CDER and CBER] will continue to consider factors such as use in previously approved products or [Generally Recognized as Safe] status as a direct food additive. Under some circumstances (e.g., similar route of administration, level of exposure, patient population, and duration of exposure) experience associated with prior use may adequately qualify an excipient.

In this case, the fact that oleic acid is so widespread in the food supply and is an approved food additive is relevant but not determinative regarding the Petition's claim that oleic acid causes local dermal irritation.[30] More persuasive is oleic acid's extensive track record as a safe inactive

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[26] For example, olive oil and peanut oil contain 60-80% oleic acid.

[27] Americans who submitted to a 3-day dietary survey by the U.S. Department of Agriculture consumed 20-30 grams/day of oleic acid. Jonnalagadda SS et al., Fatty acid consumption pattern of Americans: 1987-1988 USDA Nationwide Food Consumption Survey. *Nutrition Research* . 1995;15: 1767-1781. It is estimated that a 250 mg foil packet of Imiquimod Cream 5% manufactured with 25% oleic acid would contain only 60-70 mgs of oleic acid.

[28] See 21 CFR 314.127(a)(8)(Agency may determine whether an inactive ingredient is safe for use based on "[i]nformation submitted in the [ANDA] or any other information available to the FDA"); see also *Serono*, 158 F.3d at 1324 (citing 21 CFR 314.127(a)(8) in support of decision affirming FDA's use of animal studies to confirm safety of inactive ingredients).

[29] Available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079250.pdf .

[30] As discussed below, the Petition's claim that maximal use pharmacokinetic studies are required could be read to raise a question about the safety of systemic absorption of oleic acid. The widespread use of this ingredient in food is one factor that leads to a rejection of the suggestion that such systemic absorption would present safety issues.

ingredient in numerous topical cosmetic products over the course of many decades at concentrations up to and exceeding 25%. These facts, together with the fact that oleic acid is found (albeit in lower amounts and concentrations) in numerous previously approved drug products, carries significant weight in our determination that the safety of up to 25% oleic acid in generic imiquimod drugs may be fully qualified without the need for any of the additional safety studies discussed in the Excipients Guidance.[31]

Furthermore, any ANDA for a generic version of Aldara will contain extensive clinical safety data from a comparative clinical bioequivalence study. These data will be the Agency's best indication of whether inclusion of oleic acid in the generic product's proposed formulation causes more skin-related adverse events than the RLD. Accordingly, these data will contribute to meeting the applicant's burden of demonstrating that its substituted inactive ingredients do not affect the safety of the proposed product.

Accordingly, we conclude that an ANDA applicant could provide sufficient data and information through the normal ANDA application process to satisfy the Agency that up to 25% oleic acid in a generic version of Aldara would not pose any greater skin irritation safety risks than Aldara itself.

2. Oleic acid's properties as a penetration enhancer do not raise serious safety concerns

You claim that "oleic acid, especially in high concentrations, could increase imiquimod systemic absorption and thus affect the safety profile of an imiquimod formulation containing oleic acid" (Petition at 7).

First, we disagree that oleic acid is likely to be a more effective penetration enhancer than isostearic acid. We do not expect that oleic acid would have significantly different qualities as a penetration enhancer in imiquimod products than the ingredient it replaces, isostearic acid.[32] The chemical formula for oleic acid is $C_{18}H_{34}O_2$, while the chemical formula for isostearic acid is $C_{18}H_{36}O_2$. Both are 18-carbon length fatty acids and each has the same terminal carboxyl functional group. The primary difference between them is the cis double bond located at the middle of the carbon chain of oleic acid. Both are thought to enhance penetration of imiquimod by disrupting and thereby "fluidizing" the lipid organization of the stratum corneum (the outermost layer of skin), allowing imiquimod (a lipophilic molecule) to more readily pass through this layer into the epidermis, the site of drug action.[33] Besides these similarities, our

[31] We further discuss the Excipients Guidance, and your reliance thereon, in section II.B.1 of this response.

[32] We note that you make no specific claims to the contrary. That is, while you state that oleic acid in high concentrations "could increase imiquimod systemic absorption" (Petition at 7), you do not make any specific claims, based on clinical data or the biochemistry of the various substances involved, that a 25% oleic acid formulation should be expected to deliver more imiquimod through the lipid barrier into the epidermis than a 25% isostearic acid formulation.

[33] Aungst BJ., Structure/effect studies of fatty acid isomers as skin penetration enhancers and skin irritants. *Pharm Res* 1989 Mar; 6(3): 244-77. Kinsman DV., Isostearic and other branched acids. *J Am Oil Chem Soc.* 1979

review of the literature does not provide any reason to expect oleic acid to have greater penetration enhancing properties than isostearic acid. Accordingly, we would expect that oleic acid and isostearic acid would effect similar penetration enhancement in Aldara formulations.

Second, as we noted in our response to the Aldara BE Petition, we are not aware of any safety risks related to systemic imiquimod absorption. This is not surprising because systemic imiquimod absorption from topically applied Aldara is minimal and we have no scientific reason to suspect that this minimal absorption would be toxic. We further note that you do not make any specific claims in this regard. That is, while you state that increased systemic absorption of imiquimod could "affect the safety profile of an imiquimod formulation containing oleic acid" (Petition 7), you do not list any specific toxicity concerns. In fact, you do not even go so far as to claim that increased systemic imiquimod absorption might be unsafe. Accordingly, we conclude that even if oleic acid did have a somewhat greater penetration enhancing effect than isostearic acid, and this led to somewhat greater (but still minimal) systemic levels of imiquimod, we have no reason to think this would make an oleic acid-containing generic formulation of Aldara less safe than Aldara itself.

Finally, any ANDA for a generic version of Aldara will contain extensive safety data from a comparative clinical bioequivalence study. We have no reason to expect a generic Aldara formulation containing up to 25% oleic acid poses any greater systemic toxicity risks than the RLD. Any disparity in local toxicity would show up in these clinical safety data. If it does not, we would be further assured that inclusion of oleic acid in a generic version of Aldara does not pose any systemic toxicity concerns because imiquimod delivered from a topical cream formulation would have to be absorbed through the stratum corneum and through the underlying layers of the epidermis before it could reach the systemic circulation. Thus, systemic absorption sufficient to cause any unexpected toxicity would likely also be associated with local toxicity. Dose-limiting local toxicity has been observed in clinical studies of more frequent dosing regimens of Aldara than those approved for the treatment of AK or sBCC.

Accordingly, we conclude that an ANDA applicant could provide sufficient data and information through the normal ANDA application process to satisfy the Agency that up to 25% oleic acid in a generic version of Aldara would not pose any greater systemic toxicity risks than Aldara itself.

B. Animal and Human Safety Studies Are Not Necessary for Generic Versions of Aldara Containing Up To 25% Oleic Acid

You contend that existing data and information are insufficient to fully characterize the safety of oleic acid in concentrations up to 25% in generic versions of Aldara, and that the Agency must therefore require applicants for such products to provide additional safety data from a battery of animal and human studies (Petition at 9-15). As we have already explained, an ANDA applicant

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November; 56 (10): 823A-827A. Jenske R et al., Impact of free hydroxylated and methyl-branched fatty acids on the organization of lipid membranes. *Chem Phys Lipids*. 2008 Jul; 154 (1): 26–32. See Aldara BE Petition Response for a more extensive discussion of Aldara's method of drug action.

could provide sufficient information and data to demonstrate that oleic acid is safe for use in concentrations up to 25% in a generic version of Aldara through the normal ANDA application process. Accordingly, we further conclude that the additional studies you believe should be required need not be conducted. Nonetheless, we address your arguments regarding the need for such studies below.

1. The safety studies often required of new pharmaceutical excipients are not necessary

You contend that oleic acid, as you claim it is used in the proposed Nycomed and Perrigo products, should be considered a "new excipient" because it is "not fully qualified by existing safety data with respect to the currently proposed level of exposure, duration of exposure, or route of administration" (Petition at 10, citing Excipients Guidance at 1). That is, you contend that even though oleic acid has been used in numerous previously approved drug products, including many topical products, it has never been approved when included at such high concentrations, in such high amounts, or in this exact dosage form (a topical semi-solid cream) (Petition at 10). Accordingly, you contend that the use of oleic acid in the proposed imiquimod products must be qualified by data from numerous pharmacology, toxicology, and sensitization studies (Petition at 10).[34]

We disagree. While you rely extensively on the Excipients Guidance in arguing that oleic acid should be considered a new excipient, you fail to mention the section quoted in part A.1 above, in which the Agency explained that in some circumstances an excipient's presence in food, cosmetics, or previously approved drug products will be sufficient to fully qualify the safety of the ingredient without the need for any of the toxicology and sensitization studies you claim are necessary (Excipients Guidance at 2). As discussed in part A.1, oleic acid is not only found in numerous previously approved drug products (including many topical products, one of which, like Aldara, is a semi-solid emulsion), but is also widespread in the food supply and found in hundreds of topical cosmetic products, sometimes at concentrations up to 50%.

Also, as discussed in part II.A.1, we have concluded that an ANDA applicant could submit sufficient data and information to demonstrate the safety of up to 25% oleic acid as an excipient in generic versions of Aldara, in part because the scientific literature and agency experience support the safety of oleic acid as a general matter and in part because clinical safety data from the applicant's bioequivalence study must show that the incidence and severity of adverse events is not significantly worse for the proposed generic product than for the RLD.

[34] Specifically, you claim that the use of oleic acid in imiquimod products should be qualified by the following studies, at a minimum: (a) safety pharmacology testing; (b) acute toxicology studies; (c) studies of the absorption, distribution, metabolism, and excretion of the excipient; (d) a standard battery of genetic toxicology studies; (e) three-month repeat dose toxicology studies; (f) reproductive toxicology studies; and (g) a sensitization study (Petition at 10).

Accordingly, we need not reach the question of whether 25% oleic acid in a topical emulsion such as Aldara should be considered a "new excipient" because, regardless of our conclusion, we would not require any of the studies you request.

You note that the Agency required extensive safety studies of polyolprepolymer-2 and diethylene glycol monoethyl ether (DGME), new excipients used in Avita (tretinoin gel) 0.025% and Aczone (dapsone) Gel 5%, respectively. The examples you provide in support of your claim are inapt. While it is true that, as you note, both inactive ingredients had been used in topical cosmetic products (Petition at 10-11), they had not been used nearly as extensively as oleic acid, nor were they found in any amount in the food supply, much less approved as food additives. Most important, neither had been used in a previously approved drug product so neither had been previously examined in the Agency's investigational new drug (IND)/NDA safety review process. Accordingly, adequate data to support the use of polyolprepolymer-2 and DGME were not available, whereas an ANDA applicant could provide adequate available data and information through the normal ANDA process to support the safety of oleic acid in a generic version of Aldara.

2. Preclinical testing of the formulation and the vehicle is not necessary

You contend that, in addition to the excipient testing just discussed, applications for generic imiquimod products containing oleic acid must be supported by non-clinical safety data specific to the formulation and the oleic acid vehicle (Petition at 11-12). You state that the applications for Aczone, Avita, and Aldara included such data.

Regarding the original Aldara NDA, extensive non-clinical toxicology studies were performed to support the safety of the new drug substance, imiquimod, in the drug product. These non-nonclinical toxicology studies would also have served to qualify the use of the isostearic acid excipient in Aldara because isostearic acid was not an excipient that had been previously used in approved drug products and then-existing literature data were not sufficient to support the safety of isostearic acid. Likewise, Aczone and Avita included new excipients that had never been through the IND/NDA safety review process. In contrast, we have extensive experience and data supporting the safety of oleic acid (see part II.A.1).

Furthermore, Aczone, Avita, and Aldara were approved as NDAs, and NDA practices and procedures regarding non-clinical testing of excipients, vehicles, and formulations are of limited applicability to ANDAs. Specifically, ANDAs rely on the established clinical safety and efficacy of RLDs. Under the regulations regarding inactive ingredients in topical drug products, the Agency does not require additional safety data on inactive ingredients that differ from those in the RLD unless there is a reasonable basis to conclude that one or more of those ingredients raises serious questions of safety or effectiveness (see 21 CFR 314.127(a)(8)(ii)). For the reasons explained in part II.A of this response, an applicant for a generic version of Aldara containing up to 25% oleic acid in place of isostearic acid could satisfy its obligation to demonstrate the safety of this substitution without conducting any of the preclinical safety studies discussed in your Petition (see 21 CFR 314.94(a)(9)(v)).

Accordingly, we deny your request to require ANDAs for imiquimod products containing oleic acid to provide data from non-clinical testing of the proposed formulation and oleic acid vehicle.

3. Skin irritation and sensitization testing is not necessary

You further contend that ANDAs for generic versions of Aldara containing oleic acid must provide data from skin irritation and skin sensitization studies because "[p]roducts applied to the skin, both topical and transdermal, may cause skin irritation or sensitivity that can affect the absorption of the active ingredient and, in turn, the safety or effectiveness of the product" (Petition at 12). You also claim that for these reasons "FDA has required sponsors of proposed generic products to provide" such data (Petition at 12).

We disagree with your request that ANDAs for generic versions of topical imiquimod products containing oleic acid be required to provide data from these studies. For the reasons elaborated in part II.A, we have no serious concerns that substituting up to 25% oleic acid for isostearic acid in generic versions of Aldara would increase the generic formulations' potential to irritate or sensitize the skin above that of the RLD. Furthermore, any residual concerns in this regard would be dispelled if clinical safety data from the applicant's bioequivalence study show that the incidence and severity of adverse events is not significantly worse for the proposed generic product than for the RLD.

We also disagree that the Agency has a practice of requiring generic topical drug products to provide data from skin sensitization and skin irritation studies. We do not, and the two examples you provide — Avita and mupirocin ointment (NDA 050788) — are inapt. While the sponsors of these products sought to have them approved as ANDAs,[35] the Agency required them to be submitted as NDAs under section 505(b)(2) of the Act. Avita was required to be submitted as an NDA because, as discussed above, it contained a new excipient that had never been through the NDA safety review process. The mupirocin ointment could not be approved as an ANDA because the proposed generic product changed the lipophilic properties of the vehicle.[36] Furthermore, the mupirocin ointment also contained an inactive ingredient not found in any previously approved drug product.[37] The Agency's decision to require these NDAs — both of which contained truly new excipients and one of which (the mupirocin ointment) substantially altered the qualities of the vehicle — to include data from skin irritation and skin sensitization

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[35] You state that the generic mupirocin ointment in question (NDA 050788) was first submitted as an ANDA (Petition at 12), but this is incorrect. The same sponsor did submit an ANDA for a different generic mupirocin ointment containing the same inactive ingredients as the RLD (ANDA 065123), but the product you discuss in the Petition (NDA 050788), containing inactive ingredients that differ from those in the RLD, was never submitted as an ANDA. You correctly point out that the sponsor sought to have this product approved under the ANDA route as well, but, for reasons discussed in the text, the Agency declined this request.

[36] Compare 21 C.F.R. 314.127 (a)(8)(ii)(A) ("a change in the lipophilic properties of a vehicle" of a drug product intended for topical administration may raise serious questions of safety or efficacy).

[37] We note that this product also contained an inactive ingredient, Softisan 378, not found in any previously approved drug product.

studies is not inconsistent with our decision not to require such studies of generic versions of Aldara containing oleic acid.

Likewise, the Agency's practice of recommending or requiring skin sensitization and skin irritation studies for topical patches and transdermal products (Petition at 12-13) is not inconsistent with our decision not to require such studies of topical products in this case. Transdermal and topical patch products are more occlusive than topical products like Aldara. Furthermore, generic patches are typically manufactured using substantially different ingredients than the RLD. Also, the bioequivalence study design for transdermal products (single-dose crossover studies) does not provide adequate data on skin irritation and sensitization to support approval for long-term use. In contrast, as discussed in part II.A, the comparative clinical bioequivalence studies that must be conducted for generic versions of Aldara provide adequate data to compare the incidence of local adverse events (including skin irritation) between the generic formulation and the RLD.

Accordingly, we deny your request to require ANDAs for generic versions of Aldara containing oleic acid to provide data from skin irritation or skin sensitization studies.

4. Maximal use pharmacokinetic studies are not necessary

You note that new formulations of previously approved drug products can affect systemic absorption of the active ingredient (Petition at 14). Accordingly, you contend that an ANDA for a generic version of Aldara with a formulation different from Aldara's formulation must provide data from a "maximal use" pharmacokinetic study (a "max use PK study") in both the EGW and AK indications "to address any potential systemic toxicity issues" (Petition at 14-15). We disagree that ANDA applicants for generic versions of Aldara containing oleic acid must provide data from a max use PK study. As we explained in response to your prior petition concerning generic versions of Aldara (which made the same request concerning max use PK studies),[38] the Agency rarely requires applicants for generic topical drugs to conduct max use PK studies, although it may "where the systemic absorption of the [RLD] has been linked to adverse events based on systemic drug levels" or where there is reason to suspect that the inactive ingredients or composition of the proposed generic raises safety concerns related to systemic absorption of the drug product or any of its components (Memorandum from Douglas C. Throckmorton, Deputy Director, Center for Drug Evaluation and Research, FDA, to Janet Woodcock, Director, Center for Drug Evaluation and Research, FDA, re: Reconsideration of the approval of ANDA 077524 (May 30, 2008) (Throckmorton Memo), at 10-11).

Here we have neither concern. As noted previously, we are not aware of any safety issue related to systemic imiquimod absorption,[39] and we have no scientific reason to be concerned that such

[38] See Aldara BE Petition Response at pages 20-21.

[39] As the Aldara label indicates, imiquimod treatment may be associated with "flu-like systemic signs and symptoms including malaise, fever, nausea, myalgias and rigors" in a very small percentage of patients, but there is no evidence that this reaction is dose-dependent (i.e., there is no scientific basis to believe that the incidence of these adverse events correlates with systemic imiquimod blood levels). The reported flu-like signs and symptoms may

issues may arise as a result of substituting oleic acid for isostearic acid. In fact, the Petition itself does not discuss or even mention a single specific safety concern related to systemic exposure of imiquimod (or oleic acid, or any other inactive ingredient that might be found in any generic imiquimod formulation). Furthermore, every ANDA for a generic imiquimod cream must contain data from at least one clinical bioequivalence study in which the safety profile of the generic and RLD are compared. As discussed above in part II.A.2, any disparity in local toxicity should show up in these clinical safety data. If no disparity is shown in that testing, we would be further assured that inclusion of oleic acid in a generic version of Aldara does not pose any systemic toxicity concerns because imiquimod delivered from a topical cream formulation would have to be absorbed through the stratum corneum and underlying layers of the epidermis before it could reach the systemic circulation. Thus, systemic absorption sufficient to cause any unexpected systemic toxicity would likely also be associated with local toxicity.[40] Accordingly, we do not believe the use of up to 25% oleic acid in generic versions of Aldara would raise any "potential systemic toxicity issues" that need to be addressed through max use PK studies.[41]

The examples you cite in support of a blanket requirement that all generic versions of Aldara with formulations differing from Aldara must conduct max use PK studies are unpersuasive (Petition at 14-15). First, the fact that we required max use PK studies for Avita and have recommended that max use PK studies be conducted in support of Graceway's application for a lower strength imiquimod product is not pertinent because those products were submitted as NDAs, not ANDAs. The Agency requires sponsors of NDAs for topical drug products to submit data from max use PK studies to help establish product safety and to characterize any differences in systemic exposure related to different dosing regimens and/or different concentrations of the active ingredient. As explained in part I.B of this response, however, applicants for generic versions of already-approved drugs generally do not have to independently establish the safety and efficacy of their proposed products. Applicants for topical generic drugs must characterize any formulation differences and demonstrate that they do not impair the safety or efficacy of the product (21 CFR 314.94(a)(9)(v)), but the Agency exercises considerable flexibility regarding exactly what demonstration must be made. As already explained, there is no standing requirement that applicants for generic topical products provide data from max use PK studies simply because they have different inactive ingredients from the RLD. More important, we have no scientific reason to require such data from applicants proposing generic versions of Aldara that substitute oleic acid for isostearic acid.

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represent a more intense immune response experienced by a small number of subjects following dermal exposure to the drug.

[40] We further note, as we did in response to the Aldara BE Petition, that it is difficult to imagine a scenario where a serious adverse event caused by a generic formulation of Aldara could be detected in a max use PK study (which typically enrolls a very small number of individuals, often no more than 10-20 per treatment arm) but remain undetected in a comparative clinical bioequivalence study (which typically involves 200-300 individuals per treatment arm).

[41] Of course, if a proposed generic version of Aldara contained one or more inactive ingredients that raised systemic toxicity concerns, the Agency might require max use PK studies. Such a determination will be made during the normal course of our review of any application.

Next, the Agency's discussion in the Efudex matter of whether max use PK studies should be required for generic 5% fluorouracil creams also does not support your position. In the Efudex matter, the active ingredient, 5-flourouracil, was used in both a topical drug product (Efudex) and as a component of an intravenously administered combination product. As one would expect, systemic absorption of 5-flouroracil was much higher from intravenous injection than topical application — as much as 22,000 times higher (Throckmorton Memo at 10). Because even those levels of systemic absorption were deemed generally safe, we were assured that Efudex presented minimal systemic toxicity risk. But even though we do not have similar data regarding systemic absorption of imiquimod from intravenous injection, we are nonetheless confident that the levels of systemic imiquimod absorption associated with the topical application of Aldara or any generic version of Aldara (which is required to contain the same amount of the active ingredient imiquimod as Aldara) are minimal and this minimal absorption is not toxic.[42]

Because we conclude that there is no need, as a general matter, for ANDAs for generic versions of Aldara to include data from any max use PK studies, we need not address your further argument that such studies would need to be conducted in both the EGW and AK indications (Petition at 15-17).

Accordingly, we deny your request.

C. Applications for Generic Versions of Aldara Containing Oleic Acid in Place of Isostearic Acid May Be Submitted as 505(j) Applications

As discussed above in part II.B, you contend that an application for a generic version of Aldara containing oleic acid (and possibly other ingredients) in place of isostearic acid must include data from a number of animal and human clinical studies to demonstrate the safety of the proposed product. You further contend that because such studies go beyond "limited confirmatory testing" of the type that may be conducted in support of an ANDA, the Agency must refuse ANDAs for such products and require applicants to submit applications under section 505(b)(2) of the Act instead (Petition at 2, 15-16). We disagree.

As explained above, we do not believe, as a general matter, that an application for a generic version of Aldara containing oleic acid in place of isostearic acid will need to include data from any of the animal and human studies you contend should be required. Rather, we think an applicant for such a product can satisfy its obligation to demonstrate that oleic acid does not affect the safety (or efficacy) of the proposed product through the normal ANDA application process, which includes the submission of clinical safety data collected from a comparative clinical bioequivalence study. Accordingly, we need not consider whether any of the additional studies you believe should be required would fall within the category of "limited confirmatory testing."

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[42] In contrast, where we do have reason to believe systemic absorption may be related to toxicity, we may require max use PK studies of proposed generic drug products.

The examples you offer in support of your position — Avita and mupirocin ointment (NDA 050788) — are unpersuasive. While it is true that the sponsors of these products sought to have them approved as ANDAs,[43] and the Agency required them to be submitted as NDAs under FDCA section 505(b)(2), the circumstances were not similar. As discussed in part II.B.3, both Avita and the mupirocin ointment contained truly new excipients that had never been through the NDA safety review process. Furthermore, the mupirocin ointment could not be approved as an ANDA because the proposed product substantially altered the chemical properties of the vehicle. Here, oleic acid is a well-known excipient used in numerous previously approved drug products and is not expected to change the chemical properties of the vehicle used in the Aldara formulation. Accordingly, our decision to require those products to proceed as 505(b)(2) applications is not inconsistent with our decision not to require such studies of generic versions of Aldara containing oleic acid.

We therefore deny your request that the Agency require any application for a generic version of Aldara that substitutes oleic acid for isostearic acid to be submitted under section 505(b)(2) of the Act.

III. CONCLUSION

For the reasons discussed above, the Petition is denied.

Sincerely,

Janet Woodcock
Director
Center for Drug Evaluation and Research

[43] You state that the generic mupirocin ointment in question (NDA 050788) was first submitted as an ANDA (Petition at 12), but this is technically incorrect. The sponsor asked the Agency whether the product could be approved under the ANDA route, and the Agency said that it could not be, for the reasons discussed in the text. We note that the same sponsor did submit an ANDA for a *different* generic mupirocin ointment (ANDA 065123), but the product you discuss in your Petition (NDA 050788) was never submitted as an ANDA.